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Case review

Sudden cardiac death from parvovirus B19 myocarditis in a young man with Brugada syndrome

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ABSTRACT

Cardiovascular diseases are the leading cause of sudden death all over the world. The aetiology of sudden cardiac death among young adults includes Brugada syndrome and myocarditis.

Brugada syndrome is a genetic abnormality of sodium channels in the myocardium with a characteristic electrocardiographic pattern.

Myocarditis has several aetiologies including infections. One of the most common cardiotropic viruses is parvovirus B19. This infection presents as a febrile illness in childhood and may result in fatal outcome, more frequently in adults. In this report we present a case of a young man who suffered from a mild upper respiratory tract infection. After recovery he had an episode of syncope and was diagnosed with Brugada syndrome. Some weeks later he died suddenly at home while sleeping. The detailed forensic pathological, histological and microbiological investigation revealed a parvovirus B19-associated myocarditis. Synergic effect of structural and functional abnormalities of the myocardium may lead to death. The cause and potential complications (eg. myocarditis) of even mild infections should be monitored carefully.

1. Introduction

Cardiovascular diseases are the most important causes of the sudden death.[1]

The male gender is present in 67% of sudden cardiac death (SCD) cases. Among children and young adults the most important causes of SCD are inherited cardiomyopathies, primary electrophysiological disorders (such as long QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia) and myocarditis.[2,3]

Myocarditis may be responsible for the sudden cardiac death of young people in 8–12% up to 42%. It has several aetiologies including infections. Viral presence ranges from 19 to 67% in adult and paediatric cases.[4,5]

The most frequent cardiotropic viruses are the coxsackie virus, adenovirus, parvovirus B19, human herpesvirus 6, Epstein–Barr virus, cytomegalovirus and hepatitis C virus.[6,7]

Parvovirus B19 infection – also known as erythema infectiosum or fifth disease – is usually asymptomatic or presents as a nonspecific febrile illness in childhood. Other clinical entities that are associated with this infection are arthropathy, hepatitis, erythrocyte aplasia, anaemia, hydrops fetalis, myocarditis. The clinical course in adults may differ from that in children, and the complications may be even more serious. Approximately 50–60% of the adults are seropositive for parvovirus B19-specific IgG antibodies.[5,8] Parvovirus-associated myocarditis in immunocompetent adults is extremely rare.[9]

Genetic abnormality of sodium channels in the myocardium was first described in 1992 as Brugada syndrome with a characteristic electrocardiographic (ECG) pattern: right bundle-branch block, ST segment elevation in precordial leads and high incidence of sudden cardiac death due to ventricular fibrillation. The disease is inherited showing an autosomal dominant trait in 30% of cases, in 20% no clear pattern of inheritance was noticed and the remaining 50% is

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sporadic. Brugada syndrome alone may be responsible for about 12% of sudden cardiac cases and 20% of those postmortem cases where the heart appears morphologically normal.[10,11]

In this article we report a sudden death of an immunocompetent young male who was previously suffered from a mild upper respiratory tract infection and in the reconvalescent period he was diagnosed with Brugada syndrome. Two and a half months following the infection he died suddenly due to an acute parvoviral myocarditis.

2. Case report

2.1. Medical history

A 22-year-old young man was found dead in his bedroom by his mother. The body was lying next to the bed and a little amount of blood was on the floor. The emergency service arrived soon after, but because of the signs of the early death, livor and rigor mortis, reanimation was not started. A lacerated wound and blood was

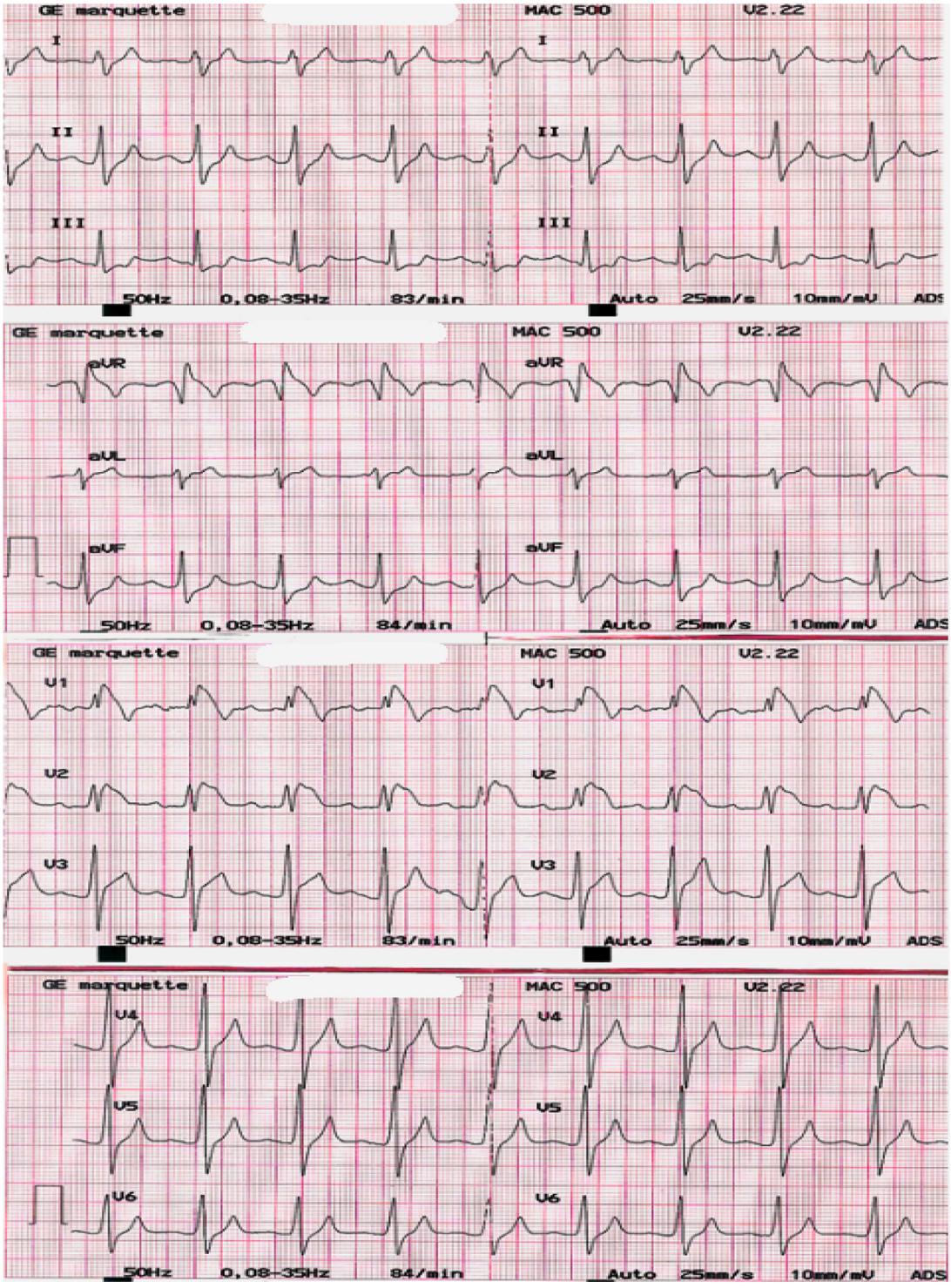

Fig. 1. ECG recorded soon after the syncope showing a typical pattern for Brugada syndrome.

noticed on his lower lip and maybe resulted from a fall when he lost consciousness before death. As it turned out the young man was under a cardiological investigation because of repolarisation disturbances found earlier on ECG. Appoximately two and a half months prior his death he had flu-like symptoms, fever, cough, sore throat. During a routine blood test an episode of syncope occurred. Immediately after the syncope an ECG was recorded that revealed a typical pattern for Brugada-syndrome (Fig. 1). His routine blood test results were negative except for a slight lympho-monocytosis. The throat culture was negative for bacteria and fungi. The cranial computed-tomography, chest X-ray and the magnetic resonance imaging (MRI) of the heart were all unremarkable. The echocardiography did not show any structural changes. An implantable cardioverter-defibrillator (ICD) was offered but he refused the implantation. He did not take any medicines, and previously not other chronical disease was noticed in the medical records. In his family there was no history of premature sudden death. After the symptoms of the upper respiratory tract infection disappeared he had a continuous fatigue and tried to spare himself. The death occurred during rest.

2.2. Autopsy findings

As the young man died at home suddenly and unexpectedly, according to the Hungarian law and local rules, the autopsy was performed at the Department of Forensic Medicine, University of Szeged with a detailed pathological examination of the body and accessory laboratory tests.

During **external examination** some red, pinpoint-sized maculopapular exanthems were found scattered in his forehead, upper extremities and chest wall. These were suspicious for an infectious disease. Around the mouth there was a little amount of dried blood due to the above mentioned lacerated wound.

The **internal examination** of the body revealed congested internal organs, splenomegaly (350 g), pulmonary oedema, hyperaemia of the lower third of trachea, fluidity of cadaveric blood.

The heart weighed 320 g, which was within a normal range, at the apex under the epicardium two pinpoint-sized petchiae were noticed. The left ventricular wall thickness was 15 mm and that of the right one was 3 mm. The valves seemed normal and the chambers were not dilated. The coronary arteries were a lit bit narrower than normal, without anomalic course and atheromatous plaques. Macroscopically there were not any pathological features on the cut surface of the myocardium.

There were not found any other morphological abnormalities of the organs during the autopsy.

Blood, and tissue samples (brain, heart including the conduction system, liver, spleen, kidneys, lungs, bone marrow) were taken for toxicological and histopathological examinations. Additional samples from the trachea, left and right lungs, left and right ventricular walls and blood were examined to detect the main cardiotropic viruses (influenza A and B viruses, adenovirus, enterovirus, parvovirus B-19, respiratory syncytial virus, cytomegalovirus, Epstein–Barr virus, herpes simplex 1 and 2 viruses) in the virological laboratory.

2.3. Toxicological results

The urine sample examined by immunochemical multidrug screening test for licit and illicit drugs (amphetamine, barbiturate, benzodiazepine, cocaine, metamphetamine, morphine, methadone, phencyclidine, tetrahydro-cannabinol/THC, tricyclic antidepressants) proved to be negative.

The blood and urine samples examined by headspace gas chromatography for alcohol provided also a negative result.

2.4. Histopathological findings

The sections were all stained by haematoxylin–eosin (HE).

Sections from the brain and lungs showed hyperaemia and significant oedema. In the kidneys, spleen and liver signs of congestion were detected. The section of the trachea showed subepithelial hyperaemia.

Sections from the right atrium, left atrium, interatrial septum showed slight fatty infiltration of myocardium (Fig. 2) and minimal grade of subendocardial fibrosis at the atrioventricular area. Around the node of sinus also a slight fatty infiltration was noticed. These findings were unusual at the age of 22.

The right ventricle and the posterior wall of the left ventricle were normal.

In the section of the anterior wall of the left ventricle a relatively large focus of massive myocardial infiltration consisting of lymphoid cells was discovered that approached also the epicardium. Small lymphocytes dominated with focal myocyte necrosis. This lesion was characteristic for a subacute myocarditis (Fig. 3).

2.5. Microbiological evaluation

The tissue samples (trachea, left and right lungs, left and right ventricular walls) were examined with real time polymerase chain reaction (RT PCR) technique for cardiotropic viruses. Parvovirus-B19 nucleic acid was found in the left ventricle, left atrium, right atrium, right lung and trachea[12] (Fig. 4).

The presence of other cardiotropic viruses were not detected in the organs and blood serum.

3. Discussion

The cause of SCD in people aged ≥35–40 years is dominantly coronary artery disease and heart failure, in younger population inherited cardiomyopathies, primary arrhythmogenic diseases. Other structural changes in the young adults like myocarditis,

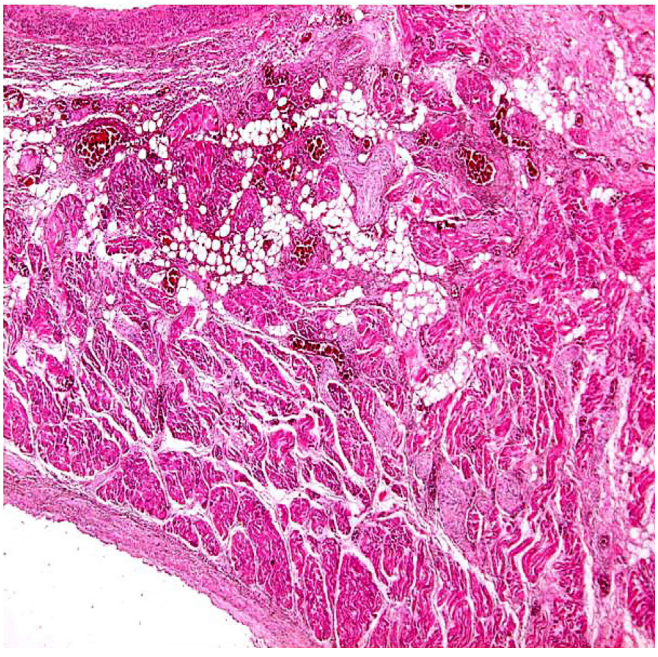

Fig. 2. Slight fatty infiltration of the right atrium and interatrial septum. (HE, 40× magnification).

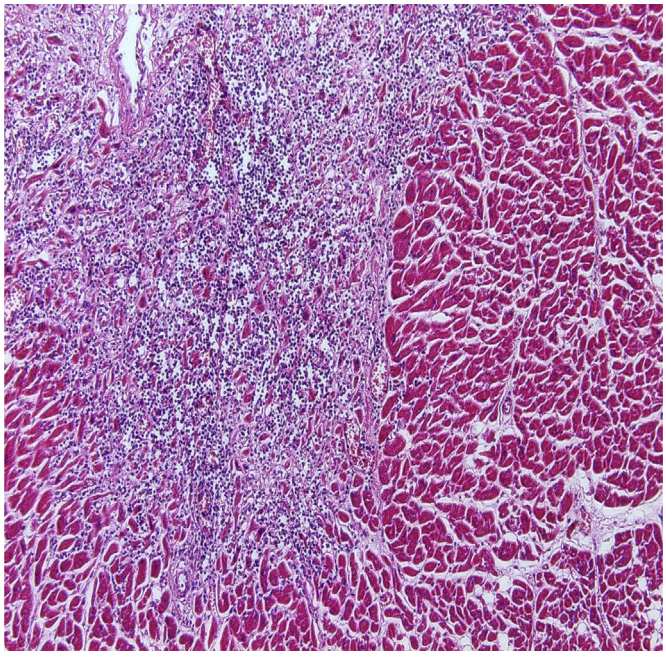

Fig. 3. Extensive infiltration of the myocardium with inflammatory cells resulting myocyte necrosis. (HE, 100× magnification).

congenital heart disease must be also taken into account. In 30% of cases no obvious cause of death is identified postmortem.[13]

A case report where a parvovirus B19 infection and an ion chanellopathy, Brugada syndrome were present at the same time with a non-witnessed fatal outcome is not common in the forensic literature. The clinical symptoms of myocarditis were not present before death, only Brugada syndrome was known from the past medical data, parvovirus-associated myocarditis was an incidental finding. Furthermore, it is also exceptional to find a published forensic autopsy case, where the infection is proven microbiologically from the tissue samples.

Buob et al. published a similar case of a 34-year old previously healthy man who had an aborted sudden cardiac death. After a successful resuscitation he was diagnosed with Brugada syndrome and a prompt implantation of ICD saved his life from further malignant arrhythmias. Moreover, in the left ventricular myocardium a localized parvovirus B19-associated myocarditis was also found by PCR technique.[14]

For practical purposes 3 types of Brugada ECG patterns are differentiated. Type 1, – corresponding to our Fig. 1 – is characterized by coved-type ST-segment elevation ≥2 mm, in more than one right precordial lead, followed by negative T wave. Only type 1 ECG pattern is regarded as the evidence of Brugada syndrome, however – as in the presented case – different types may be seen in the same subject at different times. Type 1 pattern is associated with SCN5A mutations, and this association is much stronger in cases where PQ prolongation is also present.[15] In our case the PQ was 260 ms. Recent reports also indicate, that those cases, where the coved-type ST-elevation is also present in a peripheral lead (in our case aVR) are especially prone for malignant ventricular arrhythmia (their odds ratio is increased by more than fourfold).[16]

Beyond SCN5A mutation, a genom-wide association study including 312 Brugada patients revealed two other genomic regions in connection with Brugada syndrome: rs10428132 locus in the SCN10A gene and a single-nucleotide polymorphism at rs9388451 locus, located downstream of the HEY2 gene. The loss of HEY2 gene and altered transcriptional programming during development of the heart may affect the function of sodium channels implicated in the pathogenesis of Brugada syndrome.[17]

The diagnosis of Brugada syndrome was based on the clinical symptoms and the characteristic ECG pattern in our case, genetic test was not performed.

Brugada found in his studies that many symptomatic patients had an abnormal ECG years before the symptoms appeared. Those who were resuscitated from SCD have higher risk for the recurrence of ventricular fibrillation.[11,18,19] Patients typically develop symptoms at rest or in sleep. 80% of patients with documented ventricular fibrillation had a history of syncope. Sudden death occurred in these patients mainly during early morning.[18,20,21]

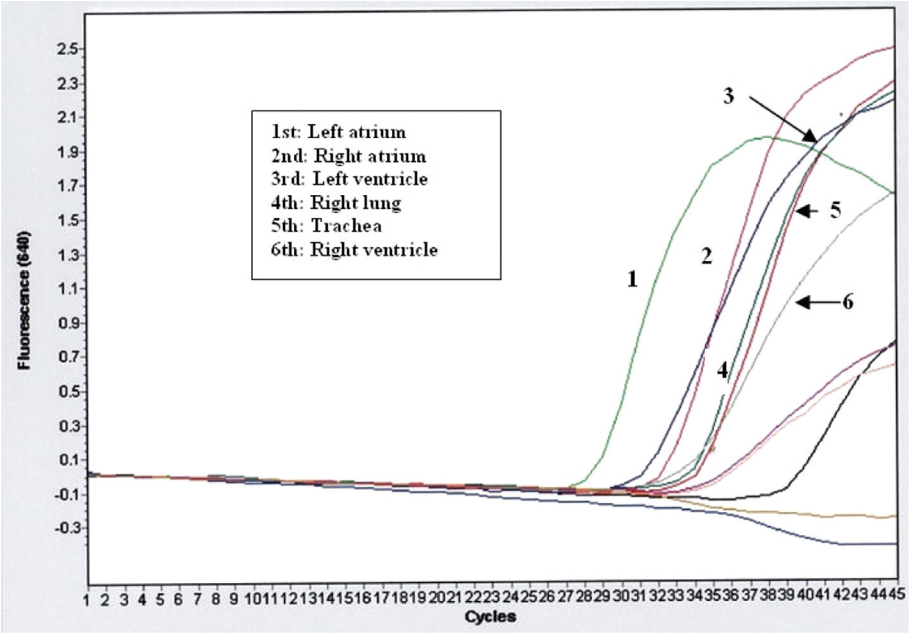

Fig. 4. Amplification curves of real time polymerase chain reaction from different organs demonstrating the presence of parvovirus B19 nucleic acid.

The spectrum of myocarditis ranges from asymptomatic or mild flu-like symptoms to fulminant haemodynamic failure and sudden death. The diagnosis is frequently made at autopsy.[4,22]

Enteroviruses are the most common cardiotropic viruses causing myocarditis at all ages, PCR identified adenovirus as the most common virus in myocarditis and in dilatative cardiomyopathy of children and young adults.[23] Besides entero- and adenoviral myocarditis parvovirus B19 should be considered as aetiology in fatal myocarditis even in adults. In Europe mainly parvovirus B19 was isolated from biopsy-proven myocarditis cases.[5] Parvovirus B19-associated myocarditis may progress to dilated cardiomyopathy. Among patients with chronic dilated cardiomyopathy parvovirus B19 genome was detected in the myocardium in 35%.[6,9]

In our case the quantity of parvovirus genome detected in the myocardium was higher than in the lung tissue and this may refer to a subacute infection.

The persistence of viral nucleic acid in the tissues (eg. myocardium) is associated with worse prognosis and PVB19-induced endothelial dysfunction can lead to a progressive impairment of left ventricular ejection fraction.[24,25]

German authors reported a case of a 5-year-old girl dying from a parvoviral myocarditis. In this case the girl was dancing and suddenly collapsed. The fatal arrhythmia was triggered by the physical activity.[26] The parvovirus B19 infection may even mimic the symptoms of acute myocardial infarction.

Kühl et al. published a study of 24 patients admitted to hospital presenting with abrupt onset of angina and symptoms mimicking myocardial infarction. Acute myocardial infarcion was excluded by coronary angiography, viral myocarditis was proved by PCR analysis in 17 patients. 50% of the myocarditis cases was caused by PVB19 (12.5% Enterovirus, 8.3% Adenovirus and 29.2% was negative) and persisted during the control biopsy in all patients. They found that persistence of virus genomes in PVB19-positive patients might be associated with the progession of the left ventricular dysfunction.[6] Molecular techniques based on amplification methods like PCR, RT PCR or nested PCR establish the diagnosis.

The gold standard in the diagnosis of myocarditis premortem is the endomyocardial biopsy and histopathological evaluation of biopsy samples.[5,27] The diagnosis of myocarditis is based on Dallas-criteria: necrosis or degeneration of myocytes and an inflammatory cell infiltrate.[28]

The macroscopic appearence of the heart is not always distinctive in myocarditis. *Corrado* et al. investigated SCD in young people. Out of the 273 cases in 76 victims (28%) he found macroscopically normal heart, 27 patient of this subgroup suffered from myocarditis. The weight of the heart ranged within normal values (230–470 g). The diagnosis was based on histological evaluation in all cases.[29]

American authors proposed a normal reference range of 223–383 g for adult male heart weight in their study investigating otherwise healthy young men aged 18–35 years who died from traumatic death.[30]

The current Hungarian clinical guideline on the diagnosis and therapy of syncope published by the Hungarian College of Cardiology does not contain the myocarditis as a potential cause of syncope. The guideline of the European Society of Cardiology published in 2009 refers myocarditis as a rare initial manifestation of syncope in young adults that raises the importance of diagnostic measures.[31]

During forensic investigation of the sudden death of an apparently healthy young individual congenital/structural (eg. inflammatory) changes as well as the possible role of cardiotoxic illicit and licit drugs like cocaine, amphetamines and anabolic steroids must always be excluded. Alcohol consumption may also provoke ventricular arrhythmias. Moreover, medications can promote acquired long QT-syndrome, therefore obtaining past medical records are important.[32]

The molecular genetic testing for cardiac diseases is unfortunately not routinely available for the forensic pathologist in Hungary.

It is very interesting that a potential synergic association between Brugada syndrome and arrhythmogenic right ventricular cardiomyopathy (ARVC) was raised by some authors, considering Brugada syndrome as an early or atypical subclinical manifestation of ARVC.[14,33] Beyond the unusual fatty infiltration in the atria and septum, typical histological signs of ARVC was not observed in our case.

In this article the coexistance of structural and functional abnormalities of the myocardium leading to the death of a young man was presented. The association between the two diseases cannot be proven exactly.

We assume that the genetically based Brugada syndrome combined with the incidental (subacute) myocarditis helped to trigger a malignant ventricular arrhythmia that resulted in the fatal circulatory collapse.

4. Conclusion

This case also emphasizes the importance of the preventive and postmortem diagnostic tools. It is estimated that the majority of cardiovascular deaths could be prevented by appropriate measures. Family members of an inherited cardiac disease patient should be screened, and an early therapy must be introduced. A thorough cardiological evaluation is always needed at a young patient presenting with syncope. The potential role of myocarditis in syncope (apart from the genetic abnormalities, eg. Brugada syndrome) and sudden cardiac death must always be taken into consideration in the clinical practice.

If parvovirus infection should occur in the family, cardiac symptoms mean a ‘red flag’ to consider a parvovirus-associated myocarditis in the background.

The additional postmortem examinations in the forensic pathology (toxicology, microbiology, histology) are essential in the investigation of sudden cardiac death to identify the cause of death and give a correct answer to the deceased’s family.

Conflict of interest

None declared.

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Ethical approval

None.

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